UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/096,500	06/12/98	ASHKENAZI A	PI1UP1

HM12/0103

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EXAMINER	
KAUFMAN, C	

ART UNIT	PAPER NUMBER
1645	9

DATE MAILED: 01/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/096,500	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *19 October 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-34 and 50-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29-34* is/are allowed.

6)☒ Claim(s) *15-28 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed October 19, 1999 has been entered.

Election/Restrictions

Applicant's election of Group II in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

Applications 60/035,496 and 60/054,885 have been considered, but will not be printed if this application issues as a patent since reference to the applications appears on a PCT instead of an issued US patent.

Sequences

When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and a sequence identifier ("SEQ ID NO:X") must be used either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02. In the instant application, a sequence identifier must be used for the sequences appearing in Figures 1A, 1B, 2, 8 and 9.

According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. The specification recites amino acid sequences of figures, but must instead refer to appropriate SEQ ID NO. See for example page 72, line 18 and p. 79, line 11.

Appropriate correction is required.

Drawings

Figure 8 of the instant application is presented on two separate panels. 37 C.F.R. § 1.84 (u)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. The two sheets must be identified by the same number followed by a capital letter. The two sheets of drawing which are labeled "Figure 8" in the instant specification should be renumbered "Figures 8A and 8B". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (u)(1), Applicant is required to change the Brief Description of the Drawings and the rest of the specification accordingly.

Figures with multiple panels, such as Figures 11 and 12, should be referred to as, for example, "Figures 11A-11E" or the equivalent instead of "Figure 11". Correction for Figures 11 and 12 is required beginning on p. 11, line 33, through p. 12, line 14.

Specification

The disclosure is objected to because of the following informalities: ATCC deposit number should be inserted where blank spaces occur on page 54, lines 11 and 15, and page 83, lines 11-13.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-24, 28 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because

the specification, while being enabling for A) an antibody which specifically binds an Apo-2DcR polypeptide that consists of the amino acid sequence of SEQ ID NO:1 or an extracellular domain thereof consisting of amino acid residues 1 to X, wherein X is any one of amino acid residues 161-236 of the amino acid sequence of SEQ ID NO:1, B) an antibody that binds the same epitope as the antibody produced by the hybridoma cell line deposited as ATCC HB-12541, HB-12542 or HB-12543, or C) a hybridoma cell line producing the antibody of either A or B, does not reasonably provide enablement for 1) an antibody that binds an Apo-2DcR polypeptide which is not identical to SEQ ID NO:1 or 2) an antibody which binds Apo-2DcR and which is a blocking antibody or 3) a hybridoma cell line producing either the antibody of 1 or 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to an antibody that binds a polypeptide that is 95% identical to SEQ ID NO:1, which is the sequence of human Apo-2DcR, or the extracellular domain of human SEQ ID NO:1 or a hybridoma producing that antibody. The prior art does not teach an Apo-2DcR polypeptide. It does teach related polypeptides Apo-3/DR3 (Marsters et al., Curr. Biol. 6, 1996, #153 cited by Applicants, also called TRAMP in the art) and DR4 (Pan et al., Science 267, 1997, #180 cited by Applicants, also called TRAIL-1 in the art). Also taught is an antibody to Apo-3 (Marsters et al., *ibid.*, see p. 1675, 5th paragraph), but that antibody would not be expected to bind Apo-2DcR as the disclosed sequence of Apo-2DcR and Apo-3 share little identity overall as shown in Figure 2 of the instant application. Therefore, the prior art does not teach an antibody that would reasonably be expected to bind Apo-2DcR. It is acknowledged that the skill in the art is high as it relates to the discovery of TNF receptor family proteins, of which Apo-

2DcR is a member, but not as it relates to predicting sequences of the receptor proteins or, as a result, the necessary structure of an antibody that would bind an unknown sequence of a member of the receptor family. Such an unknown sequence is encompassed by the breadth allowed with 95% identity to SEQ ID NO:1.

While the specification discloses (p. 80, line 24) that 47 antibody supernatants from cells obtained from animals immunized with the extracellular domain of SEQ ID NO:1 were positive for binding to Apo-2DcR, no antibody was show to be a blocking antibody. Making an antibody that blocks the activity of the protein to which it binds is unpredictable and complex even if the regions of activity in the protein are known, which is not the case here. It was known at the time the invention was made that the ligand for Apo-2DcR (called Apo-2L or TRAIL) is involved in causing apoptotic cell death (p. 2, lines 34-36 of the specification). Applicants have shown that binding of Apo-2L by Apo-2DcR inhibits Apo-2L-induced apoptosis because the receptor has no cytoplasmic domain through which to transmit a signal to the cell (EXAMPLE 3). Finding sites which allow a binding antibody to have blocking activity (or lack thereof in this case) in the absence of structural information about the receptor besides its amino acid sequence and general domain structure would require undue experimentation without a reasonable expectation of success since so little is known about which amino acids or potential epitopes would be likely to be necessary for receptor activity.

For these reasons, it would require undue experimentation to make the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 17-24, 51 and dependent claims 16, 25-28, 50 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite because it is not clear what "binds" means. It is unclear if this term is intended to include both direct and indirect binding by the antibody.

Claim 15 is indefinite because it is unclear if the polypeptide has about 95% amino acid sequence identity with both SEQ ID NO:1 and the extracellular domain, or with only SEQ ID NO:1 and is identical to the extracellular domain. It is noted that no basis in the specification could be found for an antibody binding to a polypeptide having about 95% identity with an extracellular domain of an Apo-2DcR polypeptide. Therefore, if the former meaning discussed above is intended, then it would constitute new matter. If the later is intended, the claim should be clarified so that it is clear what the 95% identity is modifying.

Claims 17-21 are indefinite because it is unclear how an antibody can comprise an antibody. If it is intended that said antibody is a monoclonal antibody, for example in claim 16, then such rephrasing in the claims would obviate this rejection.

Claims 22-24 are indefinite because it is unclear what "the biological characteristics" are and which characteristics the claimed antibody must have. The specification does not provide a limiting definition (p. 54, lines 15-21). It is unclear if this means the claimed antibody must have all biological characteristics, including structure and function, in which case it would have to be identical to the antibody produced by the hybridoma of ATCC HB-12541 (for claim 29), and then the two claims would have the same breadth, or if only some of the characteristics, *e.g.*, certain structural or functional aspects, are meant. Because of this ambiguity, the metes and bounds of the claim are not clear.

Claim 51 is indefinite because a composition must comprise more than one component. It is unclear what the composition includes besides an Apo-2DcR antibody, and it is unclear if the antibody is an active ingredient of the composition or merely present in trace amounts. Knowing whether the antibody is critical to the composition is necessary to understand the breadth of the claim. If the antibody is the active ingredient, this rejection could be obviated by adding to the end of the claim another component (*e.g.*, a carrier) which is generally accepted in the art not to be an active ingredient.

Claim 51 recites the limitation "antibodies of claim 15" in line 3. There is insufficient

antecedent basis for this limitation in the claim. Claim 15 is drawn to an antibody--singular not plural.

Prior Art

It is also noted that while provisional priority application 60/049,911 discloses the complete Apo-2DcR protein and encoding nucleic acid, it does not disclose a specific antibody; however, the prior art of record does not teach an anti-Apo-2DcR antibody as claimed. This includes the lack of teaching of an antibody to DR4 (TRAIL-1), Apo-2 (DR5, TRAIL-2) or DcR2 (TRAIL-4), which is pertinent since disclosed antibodies 6D10.97 and IC5.24.1 bind these receptors as well as Apo-2DcR, albeit with generally lower affinity (Fig. 16).

Term Usage

It is noted that the art also refers to Apo-2DcR as TR5, TRAIL-3, TRID, LIT and DcR1.

Conclusion

Claims 29-34 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the

applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

5 Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

December 29, 1999